(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/068387 A2

(51) International Patent Classification[7]: C07D

(21) International Application Number: PCT/US02/05623

(22) International Filing Date: 25 February 2002 (25.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/272,258 28 February 2001 (28.02.2001) US
60/300,572 22 June 2001 (22.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

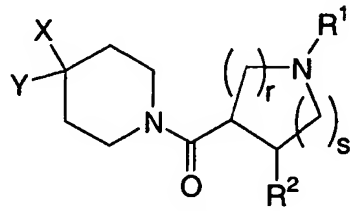
WO 02/068387 A2

(54) Title: ACYLATED PIPERIDINE DERIVATIVES AS MELANOCORTIN-4 RECEPTOR AGONISTS

(57) Abstract: Certain novel 4-substituted N-acylated piperidine derivatives are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

s is 0, 1, or 2;

n is 0, 1 or 2;

p is 0, 1, or 2;

R^1 is selected from the group consisting of

hydrogen,

amidino,

C_{1-4} alkyliminoyl,

C_{1-10} alkyl,

$(CH_2)_n$-C_{3-7} cycloalkyl,

$(CH_2)_n$-phenyl,

$(CH_2)_n$-naphthyl, and

$(CH_2)_n$-heteroaryl wherein heteroaryl is selected from the group consisting of

(1) pyridinyl,

(2) furyl,

(3) thienyl,

(4) pyrrolyl,

(5) oxazolyl,

(6) thiazolyl,

(7) imidazolyl,

(8) pyrazolyl,

(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
(12) pyrazinyl,
(13) pyridazinyl,
(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
(17) benzofuryl,
(18) benzothienyl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^2 is selected from the group consisting of
phenyl,
naphthyl, and
heteroaryl wherein heteroaryl is selected from the group consisting of
(1) pyridinyl,
(2) furyl,
(3) thienyl,
(4) pyrrolyl,
(5) oxazolyl,
(6) thiazolyl,
(7) imidazolyl,
(8) pyrazolyl,
(9) isoxazolyl,
(10) isothiazolyl,
(11) pyrimidinyl,
(12) pyrazinyl,
(13) pyridazinyl,

(14) quinolyl,
(15) isoquinolyl,
(16) benzimidazolyl,
(17) benzofuryl,
(18) benzothienyl,
(19) indolyl,
(20) benzthiazolyl, and
(21) benzoxazolyl;

in which phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3;

R^3 is selected from the group consisting of
C_{1-6} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
halogen,
OR^4,
$(CH_2)_nN(R^4)_2$,
$(CH_2)_nC{\equiv}N$,
CO_2R^4,
$C(R^4)(R^4)N(R^4)_2$,
NO_2,
$(CH_2)_nNR^4SO_2R^4$
$(CH_2)_nSO_2N(R^4)_2$,
$(CH_2)_nS(O)_pR^4$,
$(CH_2)_nNR^4C(O)N(R^4)_2$,
$(CH_2)_nC(O)N(R^4)_2$,
$(CH_2)_nNR^4C(O)R^4$,
$(CH_2)_nNR^4CO_2R^4$,
CF_3,
CH_2CF_3,
OCF_3, and

OCH_2CF_3;

in which heteroaryl is as defined above; phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and $(CH_2)_n$ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of

hydrogen,

C_{1-6} alkyl,

$(CH_2)_n$-phenyl,

$(CH_2)_n$-naphthyl, and

$(CH_2)_nC_{3-7}$ cycloalkyl;

wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

each R^5 is independently selected from the group consisting of

hydrogen,

C_{1-8} alkyl,

$(CH_2)_n$-phenyl,

$(CH_2)_n$-naphthyl,

$(CH_2)_n$-heteroaryl, and

$(CH_2)_nC_{3-7}$ cycloalkyl;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo; or two R^5 groups together with the atom to which they are attached form a 5- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

X is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCON(R^5R^5)$,
$(CH_2)_nCO_2R^5$,
$(CH_2)_nCOR^5$,
$(CH_2)_nNR^5C(O)R^5$,
$(CH_2)_nNR^5CO_2R^5$,
$(CH_2)_nNR^5C(O)N(R^5)_2$,
$(CH_2)_nNR^5SO_2R^5$,
$(CH_2)_nS(O)_pR^5$,
$(CH_2)_nSO_2N(R^5)(R^5)$,
$(CH_2)_nOR^5$,
$(CH_2)_nOC(O)R^5$,
$(CH_2)_nOC(O)OR^5$,
$(CH_2)_nOC(O)N(R^5)_2$,
$(CH_2)_nN(R^5)(R^5)$, and
$(CH_2)_nNR^5SO_2N(R^5)(R^5)$;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo; and

Y is selected from the group consisting of
C_{1-8} alkyl,
C_{2-6} alkenyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl, and

$(CH_2)_n$-heterocyclyl;

wherein heteroaryl is as defined above; phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

2. The compound of Claim 1 wherein R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, $(CH_2)_{0-1}C_{3-6}$ cycloalkyl, and $(CH_2)_{0-1}$-phenyl; wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

3. The compound of Claim 1 wherein R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3.

4. The compound of Claim 3 wherein R^2 is phenyl optionally substituted with one to three groups independently selected from R^3.

5. The compound of Claim 1 wherein X is selected from the group consisting of

C_{1-6} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC(O)N(R^5)(R^5)$,
$(CH_2)_nCO_2R^5$,
$(CH_2)_nS(O)_pR^5$,
$(CH_2)_nOR^5$,
$(CH_2)_nNR^5C(O)R^5$, and
$(CH_2)_nNR^5SO_2R^5$;

wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R^3; alkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo; and the

$(CH_2)_n$ group is optionally substituted with one to three groups independently selected from R^4, halogen, $S(O)_pR^4$, $N(R^4)_2$, and OR^4.

6. The compound of Claim 5 wherein X is selected from the group consisting of

C_{1-6} alkyl,
$(CH_2)_{0-1}$-phenyl,
$(CH_2)_{0-1}$-heteroaryl,
$(CH_2)_{0-1}$-heterocyclyl,
$(CH_2)_{0-1}NHC(O)R^5$,
$(CH_2)_{0-1}CO_2R^5$, and
$(CH_2)_{0-1}C(O)N(R^5)(R^5)$;

wherein phenyl and heteroaryl are optionally substituted with one to three groups independently selected from R^3; and alkyl and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

7. The compound of Claim 6 wherein heteroaryl is selected from the group consisting of pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl.

8. The compound of Claim 1 wherein Y is selected from the group consisting of

C_{1-8} alkyl,
C_{2-6} alkenyl,
$(CH_2)C_{3-8}$ cycloalkyl,
(CH_2)-phenyl,
(CH_2)-naphthyl,
(CH_2)-heterocyclyl, and
(CH_2)-heteroaryl;

wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three groups independently selected from R^3; and $(CH_2)_n$ alkyl, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups independently selected from R^3 and oxo.

9. The compound of Claim 8 wherein Y is selected from the group consisting of

C_{1-8} alkyl,

C_{2-6} alkenyl,

C_{5-7} cycloalkyl, and

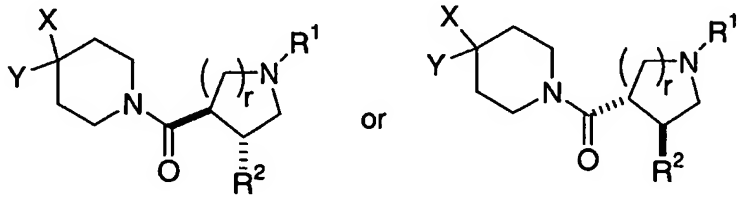
phenyl;

wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo.

10. The compound of Claim 9 wherein Y is cyclohexyl or C_{1-6} alkyl; wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo.

11. The compound of Claim 1 wherein r is 1 or 2 and s is 1.

12. The compound of Claim 1 of structural formula IIa or IIb of the indicated *trans* relative stereochemical configuration:



(IIa) (IIb)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

n is 0, 1, or 2;

p is 0, 1, or 2;

R^1 is hydrogen, amidino, C_{1-4} alkyliminoyl, C_{1-6} alkyl, C_{5-6} cycloalkyl,

$(CH_2)_{0-1}$ phenyl, or $(CH_2)_{0-1}$ heteroaryl; wherein phenyl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo;

R^2 is phenyl or thienyl optionally substituted with one to three groups independently selected from R^3;

R^3 is selected from the group consisting of

C_{1-6} alkyl,
$(CH_2)_n$-phenyl,
$(CH_2)_n$-naphthyl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
halogen,
OR^4,
$(CH_2)_nN(R^4)_2$,
$(CH_2)_nC{\equiv}N$,
CO_2R^4,
$C(R^4)(R^4)N(R^4)_2$,
NO_2,
$(CH_2)_nNR^4SO_2R^4$
$(CH_2)_nSO_2N(R^4)_2$,
$(CH_2)_nS(O)_pR^4$,
$(CH_2)_nNR^4C(O)N(R^4)_2$,
$(CH_2)_nC(O)N(R^4)_2$,
$(CH_2)_nNR^4C(O)R^4$,
$(CH_2)_nNR^4CO_2R^4$,
CF_3,
CH_2CF_3,
OCF_3, and
OCH_2CF_3;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to two substituents independently selected from halogen, hydroxy, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy; and $(CH_2)_n$ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C_{1-4} alkyl;

each R^4 is independently selected from the group consisting of

hydrogen,
C_{1-8} alkyl, and
C_{3-6} cycloalkyl;

wherein cycloalkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C_{1-4} alkyl, and C_{1-4} alkoxy;

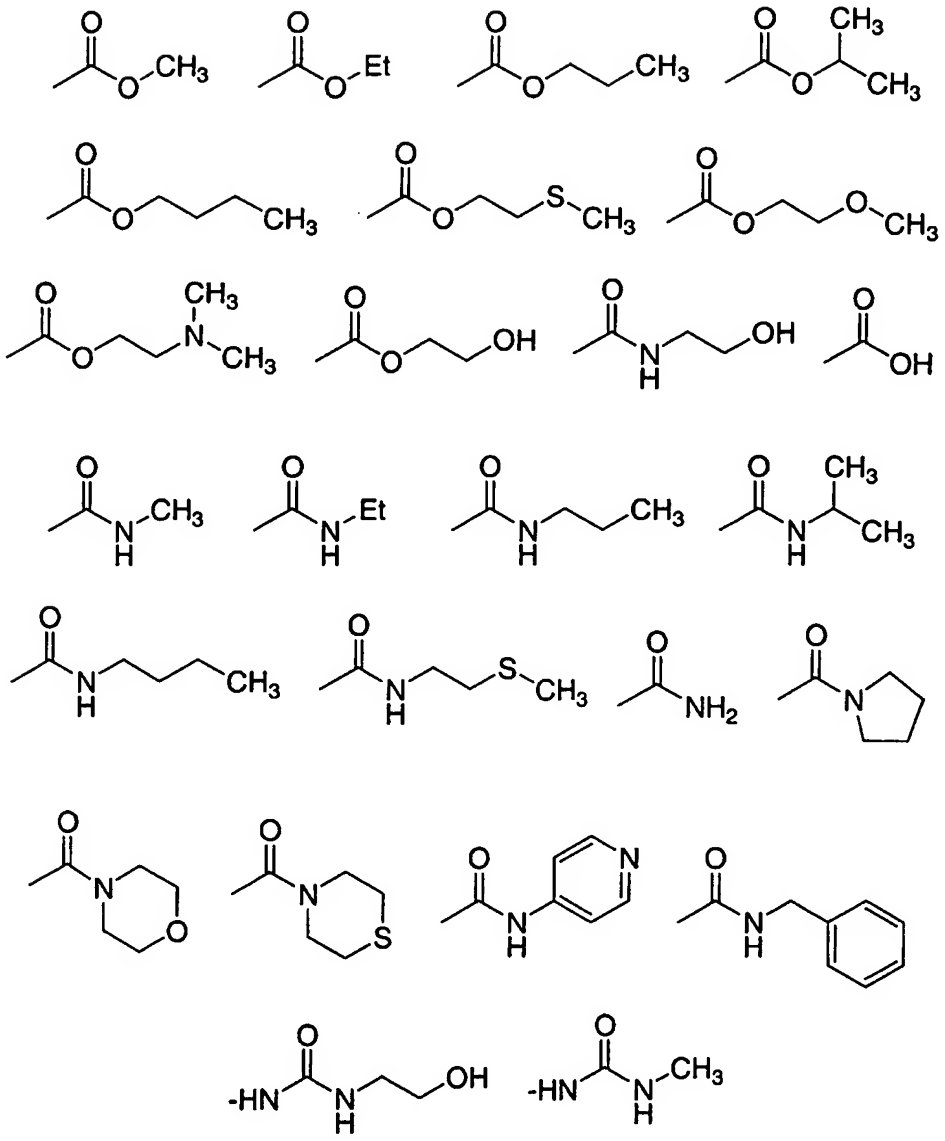
or two R^4 groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC_{1-4} alkyl;

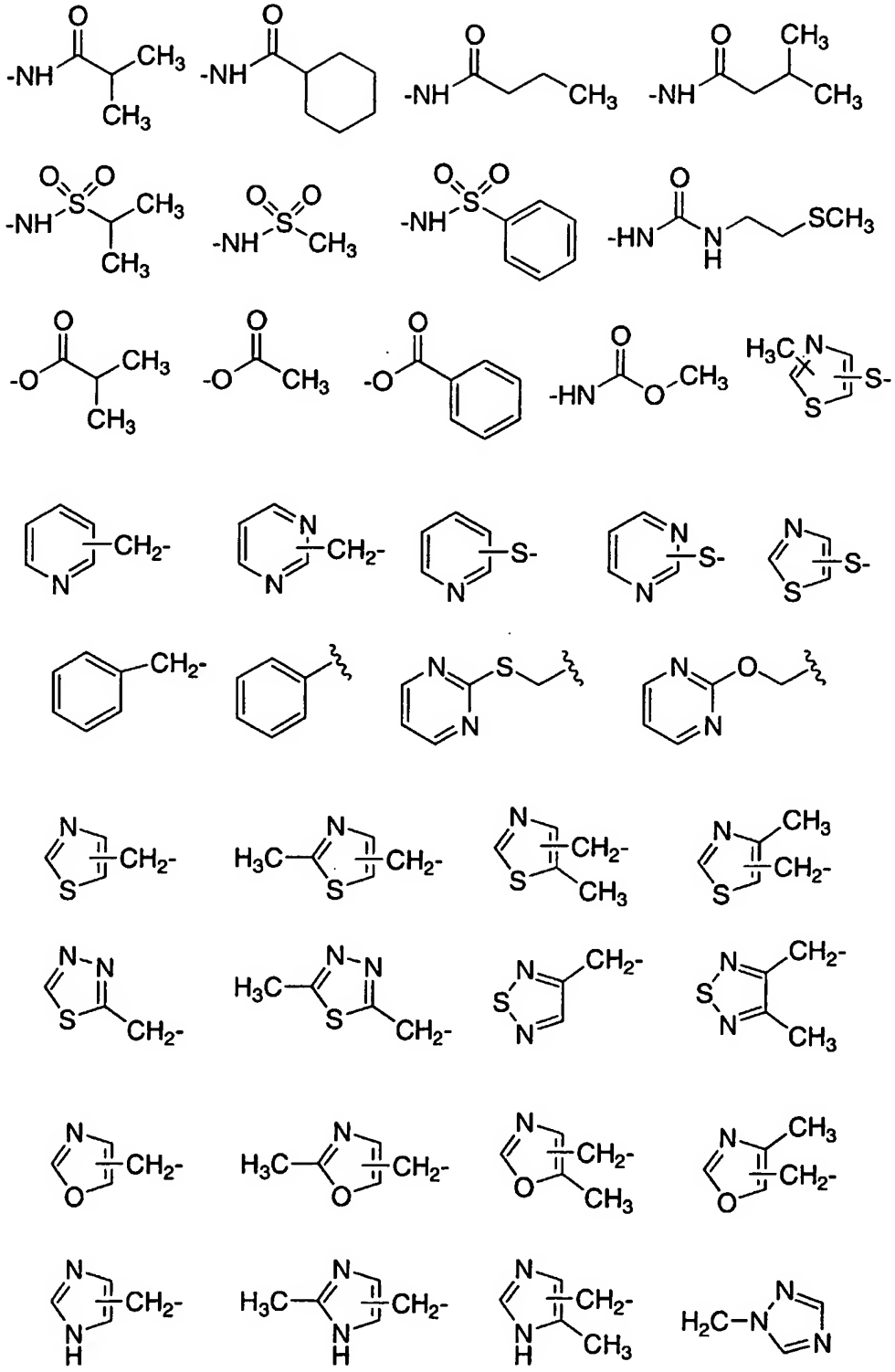
Y is selected from the group consisting of

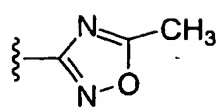
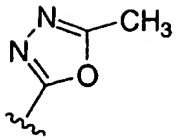
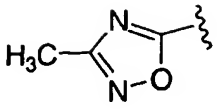
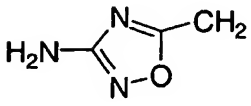
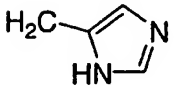
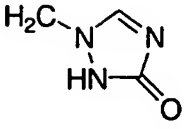
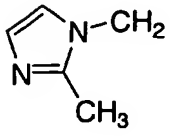
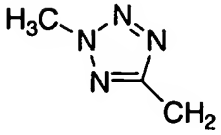
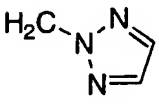
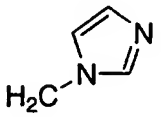
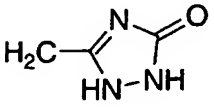
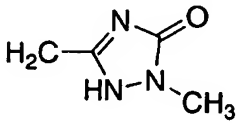
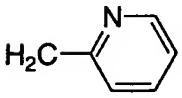
C_{1-8} alkyl,
C_{2-6} alkenyl,
$(CH_2)_{0-1}C_{3-8}$ cycloalkyl,
$(CH_2)_{0-1}$-phenyl,
$(CH_2)_{0-1}$-naphthyl, and
$(CH_2)_{0-1}$-heteroaryl;

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3; and alkyl, (CH_2), and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo; and

X is selected from the group consisting of:





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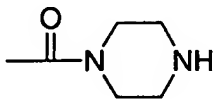
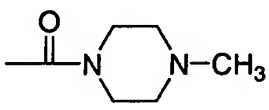
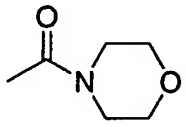
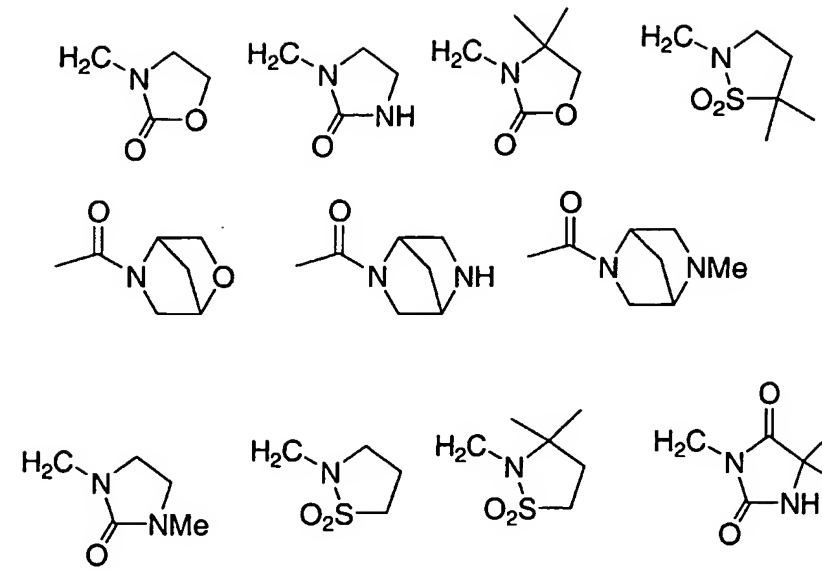
-$C(O)NHCH_2CH_2N(CH_3)_2$; $C(O)CH(CH_3)_2$; -$CH_2NHCOtBu$;

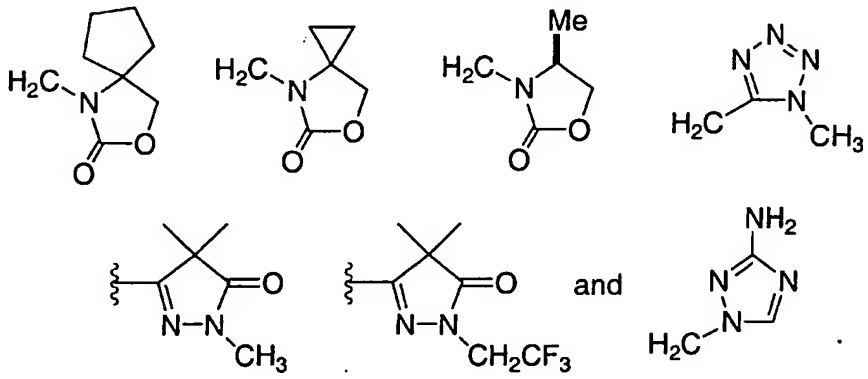
-$CH_2N(CH_3)COtBu$; -$CH_2N(iPr)COMe$; -$CH_2N(iPr)SO_2Me$;

$C(O)NHC(Me)_2CH_2OMe$; $C(O)NHC(Me)_2CH_2OH$; -$CH_2CH_2C(Me)_2OH$;

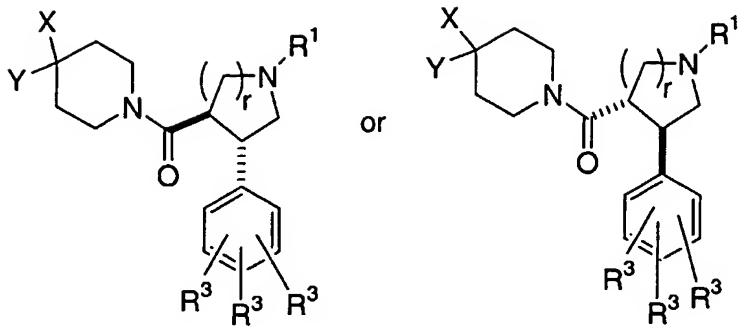






$CH_2CH_2NEt_2$; CH_2CONEt_2;



13. The compound of Claim 1 of structural formula IIIa or IIIb of the indicated *trans* relative stereochemical configuration:



(IIIa) (IIIb)

or a pharmaceutically acceptable salt thereof;

wherein

r is 1 or 2;

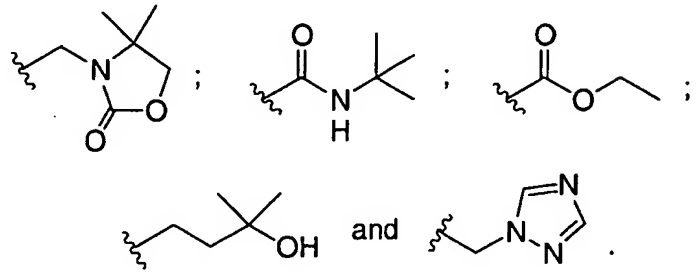
R^1 is hydrogen, C_{1-4} alkyl, or $(CH_2)_{0-1}$ phenyl;

each R^3 is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, trifluoromethyl, and C_{1-4} alkoxy;

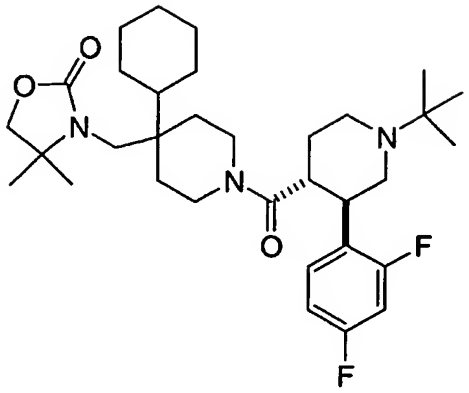
Y is cyclohexyl or phenyl; and

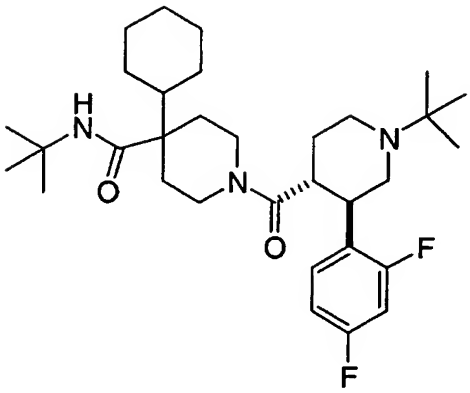
X is selected from the group consisting of

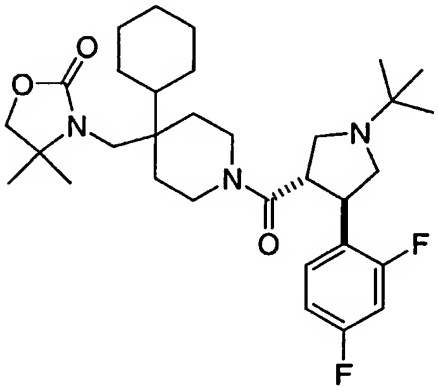
$CH_2CH_2NEt_2$; CH_2CONEt_2;

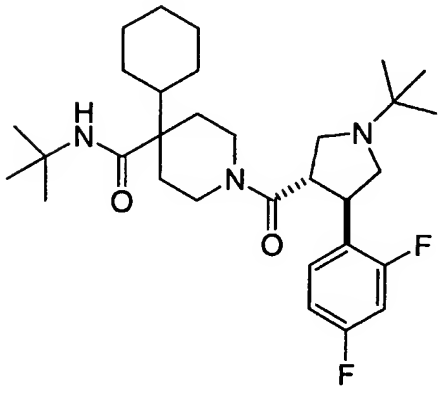


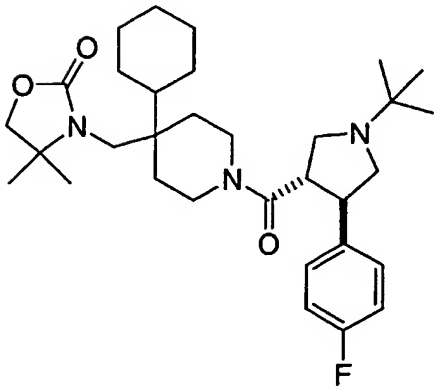
14. The compound of Claim 13 selected from the group consisting of:

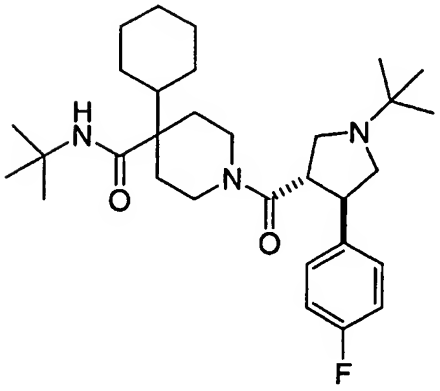


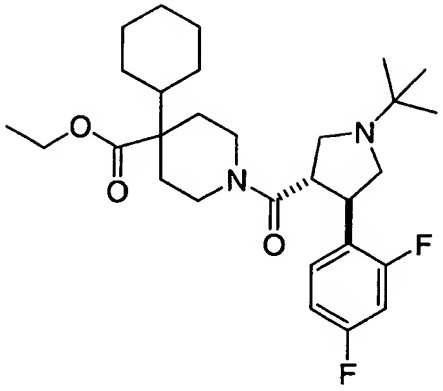


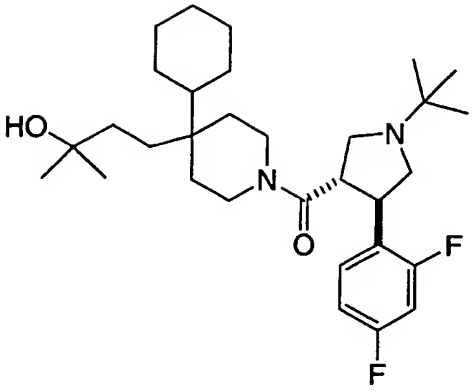


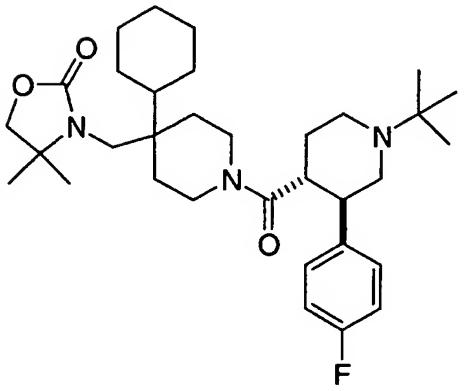


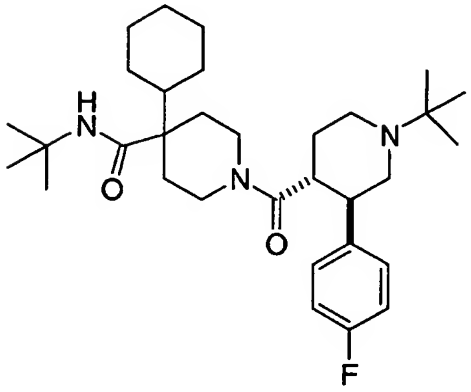


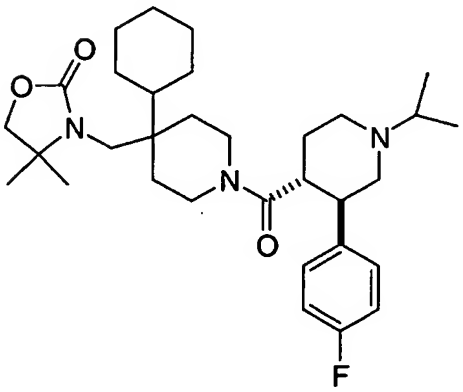


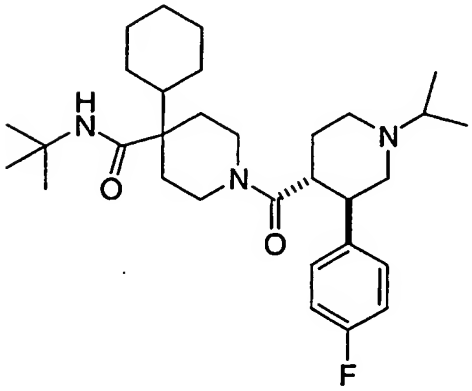


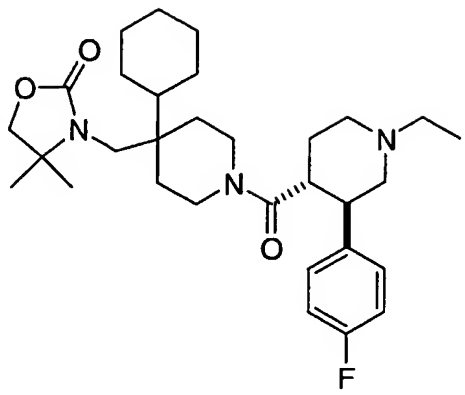


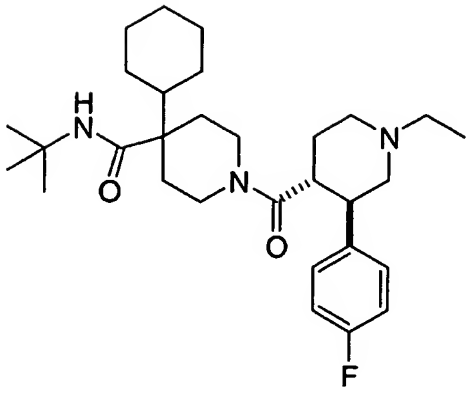


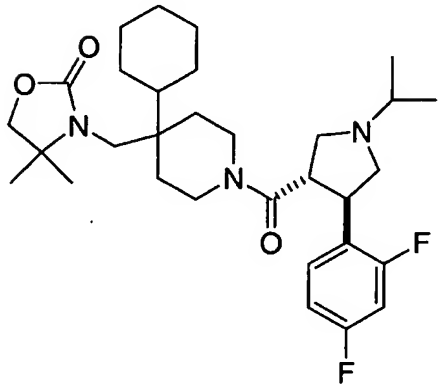


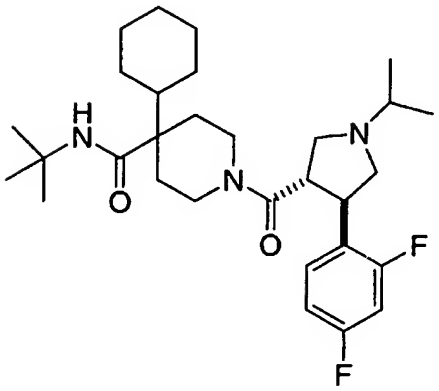


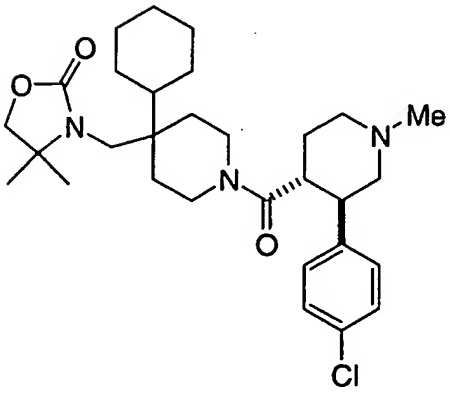


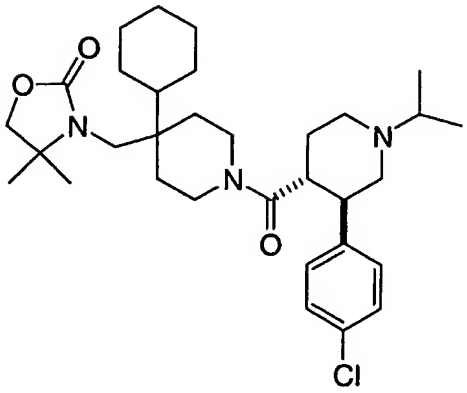


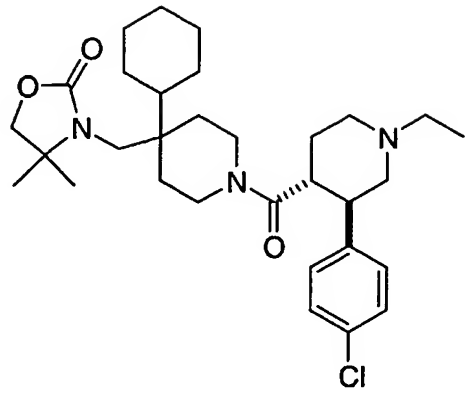


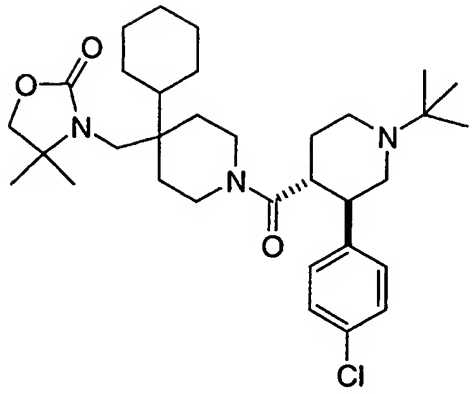


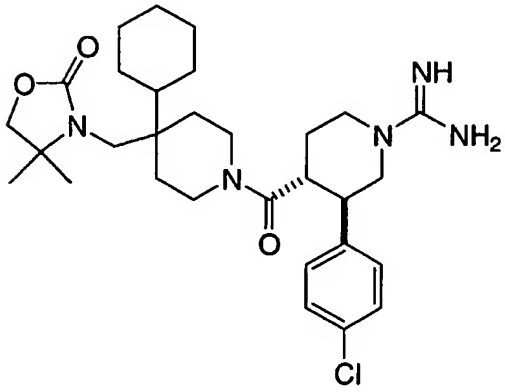


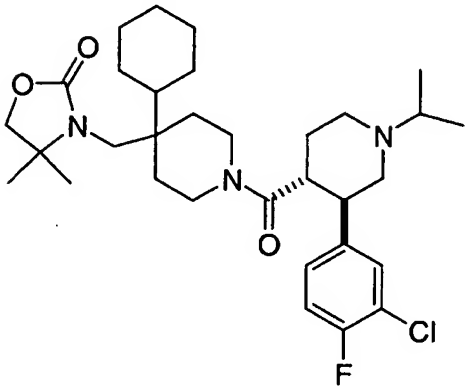


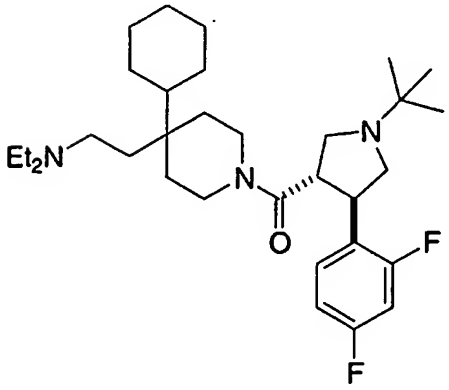


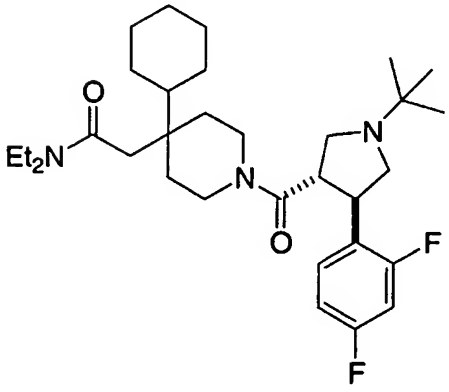


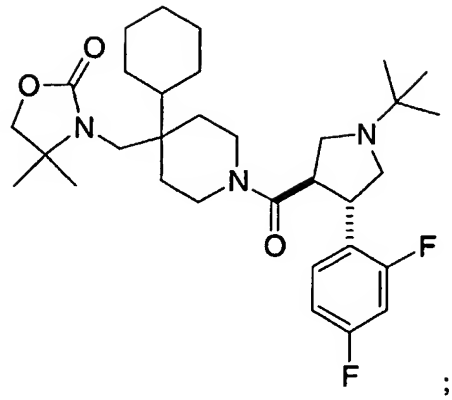










and 

;

or a pharmaceutically acceptable salt thereof.

15. A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of the melanocortin receptor in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

16. A method for the treatment or prevention of obesity in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

17. A method for the treatment or prevention of diabetes mellitus in a subject in need thereof comprising administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

18. A method for the treatment or prevention of male or female sexual dysfunction in a subject in need thereof comprising administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

19. A method for the treatment or prevention of erectile dysfunction in a subject in need thereof comprising administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

20. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of Claim 20 further comprising a second active ingredient selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, and a cannabinoid CB_1 receptor antagonist or inverse agonist.

22. The pharmaceutical composition of Claim 20 further comprising a second active ingredient selected from the group consisting of a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, and a dopaminergic agent.

23. A method of treating erectile dysfunction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 22.

24. A method of treating erectile dysfunction in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Claim 1 in combination with a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, or a dopaminergic agent.

25. A method of treating diabetes or obesity in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Claim 1 in combination with an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, an anti-obesity serotonergic agent, a β3 adrenoreceptor agonist, a neuropeptide Y1 or Y5 antagonist, a pancreatic lipase inhibitor, or a cannabinoid CB_1 receptor antagonist or inverse agonist.